

University of Groningen

Acid Catalyzed Ring-opening Reactions of Optically Pure 2-Aryl-3,3-dimethyloxetanes

Hu, Xianming; Kellogg, Richard M.

Published in:
Tetrahedron-Asymmetry

DOI:
[10.1016/0957-4166\(95\)00173-M](https://doi.org/10.1016/0957-4166(95)00173-M)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1995

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Hu, X., & Kellogg, R. M. (1995). Acid Catalyzed Ring-opening Reactions of Optically Pure 2-Aryl-3,3-dimethyloxetanes. *Tetrahedron-Asymmetry*, 6(6), 1399-1408. [https://doi.org/10.1016/0957-4166\(95\)00173-M](https://doi.org/10.1016/0957-4166(95)00173-M)

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



0957-4166(95)00173-5

Acid Catalyzed Ring-opening Reactions of Optically Pure 2-Aryl-3,3-dimethyloxetanes

Hu Xianming and Richard M. Kellogg*

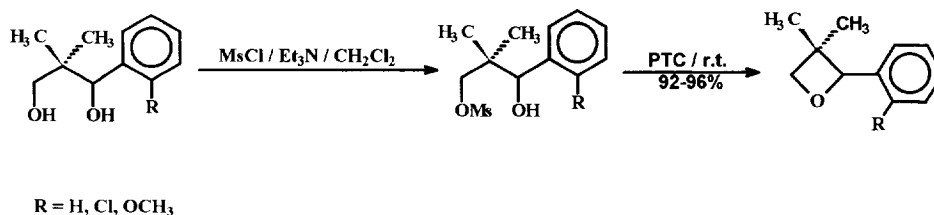
Department of Organic and Inorganic Molecular Chemistry, University of Groningen
Nijenborgh 4, 9747 AG Groningen, The Netherlands

Abstract: Some ring-opening reactions of optically pure 2-aryl-3,3-dimethyl oxetanes have been examined under strongly protic or Lewis acid conditions. Ring-opening occurred at the benzylic position and partial inversion of configuration was observed in the case of hydrolysis or alcoholysis of the optically pure oxetanes catalyzed by H_2SO_4 . The acid concentration affects the degree of inversion of configuration in water or methanol. On reaction with *n*-butyllithium or lithium thiolates aided by Lewis acid ($\text{BF}_3\cdot\text{ether}$) the corresponding β -substituted benzyl alcohols were obtained. Substitution now occurs at the least hindered carbon and the configuration of the asymmetric center remains unaffected.

Introduction

Two commonly used approaches to the synthesis of optically pure α - or β -substituted benzyl alcohols are either asymmetric reduction (stoichiometric or catalytic) of prochiral ketones with an optically active complex, or enantioselective addition of organometallic reagents to aromatic carbonyl compounds.¹⁻⁵ The generation of the stereogenic center usually does not proceed in absolute sense (100% enantiomeric purity) using such methods. A known but little used route to substituted benzyl alcohols is through the ring-opening reactions of 2,3-substituted oxetanes.⁶⁻¹² It is, however, not surprising that ring-opening reactions of optically active oxetanes have seldom been described owing to the general synthetic inaccessibility of such compounds.^{13,14} Recently we reported a convenient method to prepare a particular class of enantiomerically pure oxetanes by means of treatment of the monomethanesulfonates of enantiomerically pure 1,2-substituted 1,3-propanediols under phase transfer catalysis conditions (Eq. 1).^{15(a)}

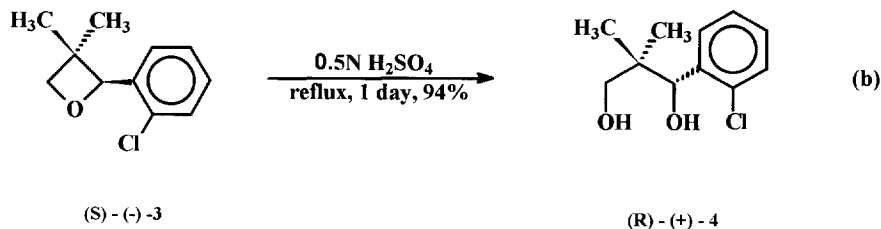
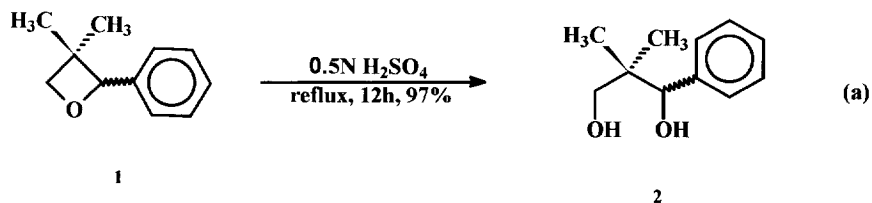
Eq. 1



We describe here a limited investigation of the acid induced ring-opening chemistry of these materials. Acid catalysis is required and the site of ring-opening depends on the reagents.

Hydrolytic ring-opening

A pertinent example of earlier work⁶ on the hydrolysis of oxetanes is that of Macchia et. al.¹⁶, who reported high syn stereoselectivity (S_N2 inversion) in the ring-opening of 6-phenyl-7-oxabicyclo[2.4.0]octane under acidic conditions at room temperature. This reaction illustrates the sensitivity of the oxetane ring system. However, when we attempted hydrolytic ring-opening of racemic 2-phenyl-3,3-dimethyloxetane **1** only 15% conversion to the corresponding 1,3-diol **2** was observed after 3 days stirring at ambient temperature in aqueous 0.5N H_2SO_4 . However, on raising the temperature to reflux after 12 hours oxetane **1** was converted to 1-phenyl-2,2-dimethyl-1,3-propanediol **2** in 97% yield (Eq. 2a).
Eq. 2



Ring-opening of optically pure (S)-(-)-2-(2'-chlorophenyl)-3,3-dimethyloxetane (S)-(-)-**3** was carried out in aqueous 0.5N H_2SO_4 at reflux for 1 day (see Eq. 2b and entry 10 in Table). There was obtained in 94% yield (R)-(+)-1-(2'-chlorophenyl)-2,2-dimethyl-1,3-propanediol (R)-(+)-**4**; this has a rotation $[\alpha]_{578} +10.8$ ($CHCl_3$), which has the opposite sign from the optically pure (S)-(-)-**3**. Optically (and enantiomerically) pure (R)-(+)-**4** has $[\alpha]_{578} +43.1$, which means that overall inversion together with racemization has taken place and that (R)-(+)-**4** has been formed in 25% optical yield. The simplest interpretation (see further) is that ring-opening occurs only at the benzylic position. When hydrolysis of optically pure (S)-(-)-**3** was carried out with H_2SO_4 (0.1N) at reflux for 1 day, the product (R)-(+)-**4** had a higher rotation, $[\alpha]_{578} +27.6$, corresponding to an optical purity of 64.0% (Table, entry 2).

For H_2SO_4 catalyzed ring-opening of 6-phenyl-7-oxabicyclo[2.4.0]octane it has been reported^{16(a)} that the stereoselectivity depends on the contact time with acid solution. As shown in the Table the ring opening of **3** itself seems to be the critical step; the temperature must be high enough (entries 3,8 and 9), and the acid strength must be sufficient (entry 1) but the contact time has little effect on the optical yields of the product **4** (entries 5-7).

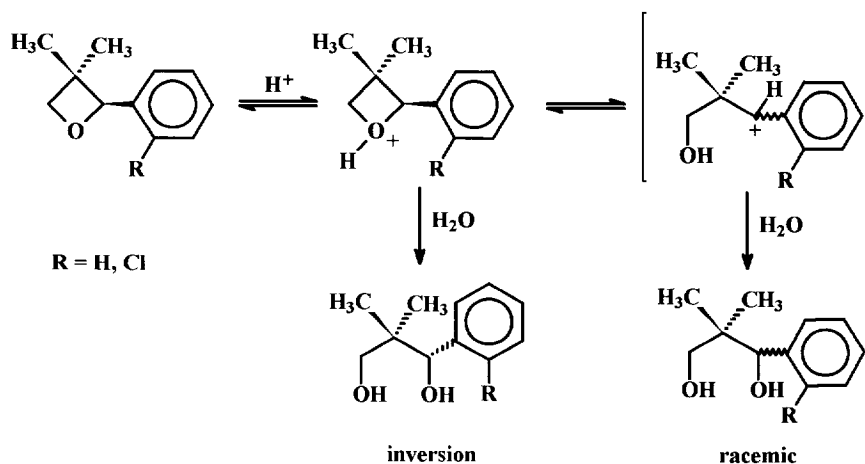
Table: Hydrolytic ring opening of (S)-(-)-3 in aqueous H₂SO₄

entry	reaction time	reaction temp.	acid conc	diol yield ^a %	[α] ₅₇₈	optical yield ^b %
1	1 day	reflux	trace	<4%		
2	1 day	reflux	0.1N	90%	+27.6	64.0%
3	3 days	R.T.	0.2N	<4%		
4	1 h	reflux	0.2N	<5%		
5	10 h	reflux	0.2N	94%	+14.3	33.2%
6	1 day	reflux	0.2N	93%	+14.0	32.5%
7	2 days	reflux	0.2N	90%	+13.2	30.1%
8	3 days	R.T.	0.5N	<10%		
9	1 day	60°C	0.5N	<10%		
10	1 day	reflux	0.5N	94%	+10.8	25.1%
11	1 day	reflux	0.5N	88%	+11.5	26.7%

- a) Isolated yields of diol (R)-(+)-4; 1-phenyl-2,2-dimethylethylene was also obtained in 3-8% yield. If the yield of 4 was less than 10%, the products were not isolated and the yields were determined by ¹H-NMR (200 MHz).
- b) Optical yields were obtained by calculation using the rotation of corresponding optically pure (R)-(+)-4, which has [α]₅₇₈ +43.1 (c=0.5, CH₂Cl₂).^{15(b)}

Investigation of the acid catalyzed hydrolysis of oxetanes has led to the suggestion of a mechanism involving preliminary equilibrium of the cyclic ether and hydronium ion with the oxonium ion, followed by a rate-determining cleavage of a carbon-oxygen bond, to form a very reactive carbonium ion.⁶ Although the point has not been examined exhaustively in this work, it would certainly appear that nucleophilic substitution with inversion can compete effectively with formation of free, achiral carbonium ions (Eq. 3).

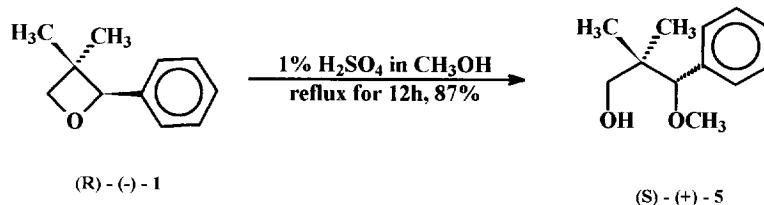
Eq. 3



Ring-opening with methanol catalyzed by H_2SO_4

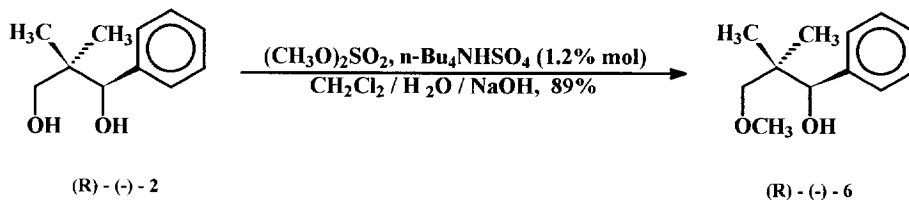
Because there is potential ambiguity in the point of attack of water, we also examined the regioselectivity and enantioselectivity of acid catalyzed methanolysis¹⁷ of optically pure 2-aryl-3,3-dimethyloxetanes. The reaction of (R)-(-)-1 with methanol in presence of 1% H_2SO_4 provided 3-methoxy-2,2-dimethyl-3-phenylpropanol (S)-(+)-5 in 87% yield (Eq. 4).

Eq. 4

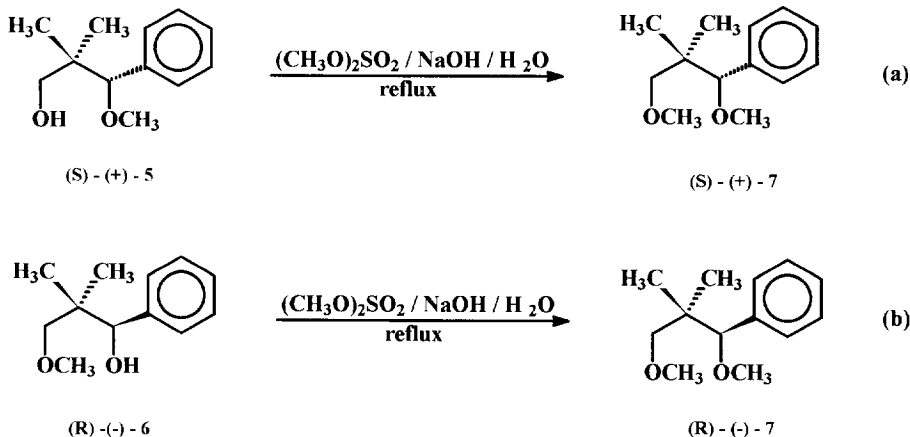


The structural assignment for (S)-(+)-5 is based on the following considerations. First (R)-(-)-6 was synthesized from (R)-(-)-2 using the phase transfer approach shown in Eq. 5. Substitution at the least hindered hydroxyl group is expected. In (R)-(-)-6 the benzylic proton absorbs at 4.50 ppm in the NMR; in starting material (R)-(-)-2 the benzylic proton is found at 4.62 ppm. However, in (S)-(+)-5 the benzylic proton is shifted significantly upfield to 4.11 ppm, consistent with alkylation at the oxygen bound to this carbon. Compound (S)-(+)-5 is known and the observed NMR data agree with those reported in the literature.¹⁸

Eq. 5



Eq. 6

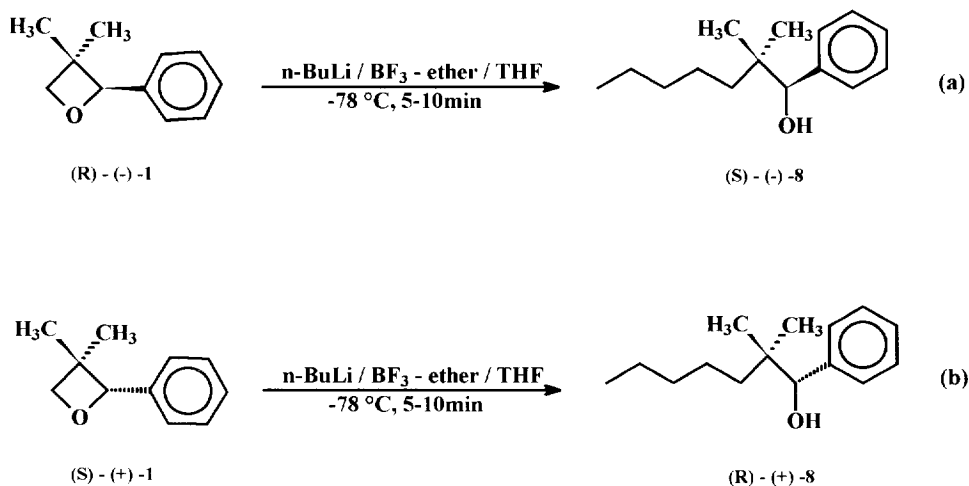


Both to establish the enantiomeric purity of (S)-(+)-**5** obtained by ring-opening and to verify the structural assignment, the experiments shown in Eq. 6a,b were carried out. Inversion of configuration at the benzylic center of **1** was expected on the basis of the hydrolysis experiments. The stereochemical correlation is given in Eq. 6 whereby the key steps are the separate conversions of (S)-(+)-**5** (Eq. 6a) and (R)-(-)-**6** (Eq. 6b) to their corresponding dimethoxy derivatives (S)-(+)-**7** and (R)-(-)-**7**. The optical purity of (S)-(+)-**5** is calculated to be 70% on the basis of the rotation observed for (S)-(+)-**7** obtained from optically pure (S)-(+)-**6**. These observations are entirely consistent with the mechanistic interpretation given in Eq. 3, wherein methanol replaces water as the nucleophile.

Lewis acid catalyzed nucleophilic ring-opening with alkyllithiums and lithium mercaptides

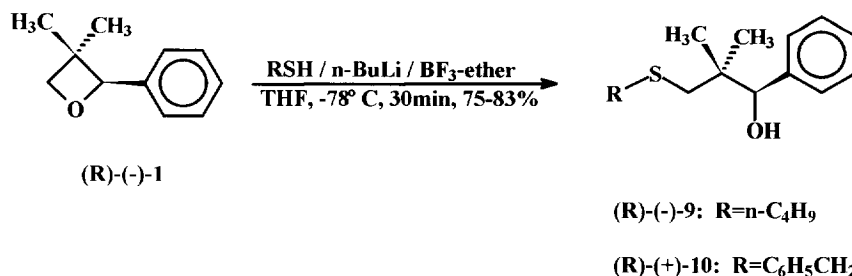
Reactions under protic conditions clearly are initiated at the benzylic (and chiral) center; preservation of stereochemical integrity is an obvious problem in such processes. Do these considerations apply to reactions with all nucleophiles? The reaction of structurally simple oxetanes with organolithium compounds has been reported to give alcohols in reasonable yields.¹⁹ However, when more hindered or multiply substituted oxetanes are allowed to react with organolithium compounds only some substituted olefins and other decomposition products are obtained.²⁰ For not heavily substituted oxetanes it is known that these problems can be circumvented by the use of Lewis acids together with the nucleophile.^{9,21} The ring opening reactions of (R)-(-)-**1** and (S)-(+)-**1** with *n*-butyl lithium in the presence of $\text{BF}_3 \cdot (\text{C}_2\text{H}_5)_2\text{O}$ in THF at -78°C gave the corresponding ring opening products, (S)-(-)-**8** (Eq. 7a) and (R)-(+)-**8** (Eq. 7b) respectively. The regioselectivity is established by the observation of the typical uncoupled low field benzylic proton, which would be absent had ring opening occurred at the benzylic position. The nucleophilic addition of alkyllithiums to oxetane using Lewis acids as activators therefore takes place between the oxygen atom and the least substituted α -carbon. The addition reaction does not affect the chiral center of the benzylic carbon atom. The examination with HPLC (chiral column) established that **8** within experimental error was enantiomerically pure. We assume that the chiral center is unaffected during ring-opening; the change in stereochemical descriptors arises from changes in the relative priority of substituents.

Eq. 7



In 1951 Searles et al.²² found that oxetanes could be cleaved by mercaptans in the presence of acids or bases or even without catalysis, although at a lower reaction rate. An attempt to cleave the ring of **1** was carried out using lithium *n*-butylmercaptide in THF at -78°C without any catalyst. No reaction took place and **1** was recovered quantitatively. When $\text{BF}_3 \cdot (\text{C}_2\text{H}_5)_2\text{O}$ was used as catalyst, the reaction with lithium *n*-butyl- and benzylmercaptide occurred smoothly in THF at -78°C . The results are shown in Eq. 8; yields of 75-83% were obtained. The configuration of the ring-opened products is again assumed to be R (retention of configuration) in view of the fact that ring-opening has occurred at the achiral center. Examination of the products (R)-(-)-**9** and (R)-(+)-**10** with HPLC (chiral column) established that the products are within experimental error enantiomerically pure.

Eq. 8



Unfortunately we had no success in obtaining ring-opening of **1** with either Grignard reagents or with amines with or without acid catalysis. We think that the cause for the different courses of ring-opening probably is steric; *n*-alkyllithiums and lithium mercaptides are probably aggregated and are effectively larger than water or methanol. This drives substitution to the least hindered position. Grignard reagents, amines and lithium amides are apparently not nucleophilic enough to initiate ring-opening.

On the basis of these limited experiments it is clear that the position of ring-opening depends on the nucleophile/acid system used. Those reactions that occur at the achiral center provide the most interesting possibilities for synthetic application.

Experimental Section

Materials and Measurements Optically pure oxetanes were obtained as described previously.¹⁵ Other chemicals used in this work were commercially available from Janssen. $^1\text{H-NMR}$ (200 MHz) and $^{13}\text{C-NMR}$ (50.3 MHz) spectra were determined on a Varian Gemini-200 system. CDCl_3 was used as a solvent and Me_4Si as an internal reference. Splitting patterns are designated as: s (singlet); d (doublet); t (triplet); q (quartet); b (broad); m (multiplet). Infrared spectra were obtained on KBr plates with a Perkin-Elmer 781 spectrometer. Mass spectra were recorded on an AEI-MS902 mass spectrometer at 70 eV. Optical rotations were measured with a Perkin Elmer Model 241 polarimeter at a concentration *c* in g/100 ml at room temperature. HPLC analyses were performed on Waters liquid chromatographic system provided with a Lambda-Max Model 480 LC spectrophotometer as well as a Hewlett Packard model HP3396A recording integrator. A chiral stationary phase column (250 x 4.0 mm) from Daicel Chemical Industries, LTD was used: conditions: 20°C , flow speed:

1ml/min, detected at 254 nm.

General procedure for the hydrolytic ring-opening of 2-aryl-3,3-dimethyloxetanes

Oxetane (5 mmol) was added to aqueous H_2SO_4 and the mixture was refluxed for a given time. Work-up was carried out after the solution had cooled to room temperature. The solution was neutralized with 20% NaOH solution and was extracted three times with dichloromethane (40 ml each time). The dichloromethane solution was dried over magnesium sulfate. The solution was evaporated under reduced pressure after filtering. The diols were obtained by bulb to bulb distillation. The purity was established by NMR and the optical rotations were determined. The results of hydrolytic ring opening of oxetanes are given in the Table.

(3S)-(+)-3-methoxy-2,2-dimethyl-3-phenylpropanol (S)-(+)-5

A solution of oxetane **(R)-(-)-1** (0.5 ml, 2.87 mmol) and H_2SO_4 in methanol (1%, 20ml) was stirred at reflux temperature for 12 hours. The mixture was neutralized with 20% NaOH after the solution had cooled to room temperature. The organic solvent was evaporated under reduced pressure and 20 ml of water was added. The solution containing product was extracted three times with dichloromethane (20 ml each time). The organic layer was separated and dried over magnesium sulfate, and the solution was filtered and evaporated under reduced pressure. The crude product contained no (NMR) unreacted oxetane. The product was purified by bulb to bulb distillation to provide 0.49g (2.5 mmol, 87% yield) of a colourless oil.

$^1\text{H-NMR}$ (CDCl_3): 0.82 (s, 3H); 0.89 (s, 3H); 2.92 (b, s, 1H); 3.21 (s, 3H); 3.43 (d, $^2J=11.1\text{Hz}$, 1H); 3.54 (d, $^2J=10.7\text{Hz}$, 1H); 4.11 (s, 1H); 7.33 (m, 5H). $^{13}\text{C-NMR}$ (CDCl_3): 19.61 (q); 22.73 (q); 39.38 (s); 57.21 (q); 71.43 (t); 91.64 (d); 127.58 (d); 127.76 (d); 128.21 (d); 138.08 (s). IR (KBr, cm^{-1}): 3440 (br,s); 3029 (w); 2971 (vs); 2933 (vs); 2875 (s); 1492 (s); 1452 (s); 1384 (m); 1361 (m); 1097 (vs); 1074 (s); 1043 (s); 742 (s); 704 (s). Exact mass for $\text{C}_{12}\text{H}_{18}\text{O}_2$ requires: M, 194.131; found: M^+ , 194.131; $[\alpha]_{\text{D}}^{25} +56.8$ (c=0.53, CHCl_3), the literature¹⁸ does not give rotation data. HPLC column: chiralcel OD, solvents: n-hexane(95%) / 2-propanol(5%).

(1R)-(-)-(1-phenyl-2,2-dimethyl-3-methoxy)propanol²³(R)-(-)-6

A solution of 50% w/w aqueous sodium hydroxide (from 10 g of NaOH and 10 g of water) was added to a solution of 3.6 g (20 mmol) of (R)-(-)-1-phenyl-2,2-dimethylpropanediol **(R)-(-)-2** and 85 mg (0.25 mmol) of tetrabutylammonium hydrogen sulphate in 40 ml of dichloromethane with vigorous stirring at room temperature. To the mixture was added dropwise over a period of 20 minutes 1.9 ml (20.2 mmol) of dimethyl sulphate; and stirring was continued for 4 hours. Concentrated aqueous ammonia (1 ml) was added and stirring was continued for a further 30 minutes to decompose excess dimethyl sulphate. The reaction mixture was poured into 50 ml of water, the organic layer was separated and was extracted once with 30 ml of dichloromethane. The organic solution was washed with water until the washings were neutral. The solution was dried over magnesium sulphate and the solvent was evaporated. The residue was distilled by bulb to bulb distillation; pure product was obtained as a colourless oil (3.46 g, 17.8 mmol, 89% yield).

$^1\text{H-NMR}$ (CDCl_3): 0.89 (s, 3H); 0.90 (s, 3H); 3.22 (d, $^2J=9.0\text{Hz}$, 1H); 3.32 (d, $^2J=9.0\text{Hz}$, 1H); 3.41 (s, 3H); 3.62 (b, s, 1H); 4.59 (s, 1H); 7.32 (m, 5H). $^{13}\text{C-NMR}$ (CDCl_3): 19.79 (q); 22.87 (q); 39.50 (s); 59.28 (q); 81.40 (q); 81.12 (t); 127.10 (d); 127.51 (d); 127.68 (d); 141.66 (s). IR (KBr, cm^{-1}): 3457 (br,vs); 3030 (m); 2962 (vs); 2876 (vs); 1478 (s); 1452 (s); 1194 (m); 1102 (vs); 1047 (s); 739 (s); 703 (s). Exact mass for $\text{C}_{12}\text{H}_{18}\text{O}_2$ requires: M, 194.131; found: M^+ , 194.131. EA, C, 74.19; H, 9.34; found: C, 74.21; H, 9.33; **(R)-**

(-)-6: $[\alpha]_{578} -29.6$ $[\alpha]_D -27.3$ ($c=0.73$, CHCl_3). HPLC column: chiralcel OD, solvents: n-hexane(97.5%) / 2-propanol(2.5%).

General procedure for the synthesis of (S)-(+)- and (R)-(-)-1,3-dimethoxy-2,2-dimethyl-1-phenylpropanes (S)-(+)-7 or (R)-(-)-7

In separate experiments 3 g (15.5 mmol) of optically pure **(S)-(+)-6**, **(R)-(-)-6** and optically impure **(S)-(+)-3-methoxy-2,2-dimethyl-3-phenylpropanol (S)-(+)-5** from the reaction of **(R)-(-)-2-phenyl-3,3-dimethyloxetane (R)-(-)-1** with methanol, were allowed to react with 3 ml (32 mmol) of dimethyl sulphate and 40% w/w aqueous sodium hydroxide (from 4 g of NaOH and 6 g of water). The reaction mixture stirred at 100 °C in oil bath for 3 hours. The mixture was allowed to cool to room temperature, 2 ml of concentrated aqueous ammonia was added, and the reaction mixture was stirred for a further 30 minutes to decompose excess dimethyl sulphate. The work-up was carried out as described above. The pure products were colourless oil (average 2.7 g, 12.9 mmol, 83% yield).

$^1\text{H-NMR}$ (CDCl_3): 0.79 (s, 3H); 0.98 (s, 3H); 2.98 (d, $^2J=8.7\text{Hz}$, 1H); 3.21 (s, 3H); 3.27 (d, $^2J=8.7\text{Hz}$, 1H); 3.36 (s, 3H); 4.17 (s, 1H); 7.31 (m, 5H). $^{13}\text{C-NMR}$ (CDCl_3): 20.55 (q); 20.93 (q); 39.64 (s); 57.29 (q); 58.99 (q); 79.78 (t); 86.99 (d); 127.13 (d); 127.51 (d); 128.39 (d); 139.10 (s). IR (KBr, cm^{-1}): 3029 (w); 2978 (s); 2929(s); 2874 (s); 1478 (w); 1452 (m); 1391 (w); 1361 (w); 1194 (m); 112 (vs); 1099 (vs); 743 (m); 704 (s). Exact mass for $\text{C}_{13}\text{H}_{20}\text{O}_2$ requires: M, 208.146, found: M^+ , 208.146; EA, C, 74.96; H, 9.68; found: C, 74.92; H, 9.65; Optically pure **(R)-(-)-7**: $[\alpha]_D -54.7$, $[\alpha]_{578} -59.6$ ($c=0.68$, CHCl_3). Optically pure **(S)-(+)-7**: $[\alpha]_D +53.3$, $[\alpha]_{578} +57.9$ ($c=0.55$, CHCl_3). Optically impure **(S)-(+)-7**: $[\alpha]_D +38.6^\circ$, $[\alpha]_{578} +41.6^\circ$ ($c=0.27$, CHCl_3). An attempt to establish the enantiomeric purity by $^1\text{H-NMR}$ (200 MHz) analysis using the chiral shift reagent tris-(d,d-dicampholylmethanato)-europium(III), $\text{Eu}(\text{dcm})_3$, (10%mol) led to small peak separations of the aromatic protons but the separation was not large enough to determine accurately the e.e.

(S)-(-)-(1,1-dimethylpentyl)-benzenemethanol (S)-(-)-8 and (R)-(+)-(1,1-dimethylpentyl)-benzenemethanol (R)-(+)-8^{13a}

Under a nitrogen atmosphere a solution of n-butyllithium (18 mmol) was added to $\text{BF}_3 \cdot \text{OEt}_2$ (9 mmol) in 20 ml of THF at -78°C ; the mixture was stirred for 10 minutes. Thereafter **(S)-(+)-2-phenyl-3,3-dimethyloxetane (S)-(+)-1** or **(R)-(-)-2-phenyl-3,3-dimethyloxetane (R)-(-)-1** (6 mmol) was added immediately. After stirring 10 minutes at -78°C , the reactions were terminated by adding aqueous ammonium chloride and workup was carried out. The mixture was extracted with chloroform and the organic materials were washed with brine and water, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by bulb to bulb distillation.

$^1\text{H-NMR}$ (CDCl_3): 0.84 (s, 3H); 0.91 (t, 6H); 1.31 (m, 8H); 1.86 (s, 1H); 4.47 (s, 1H); 7.32 (m, 5H). $^{13}\text{C-NMR}$ (CDCl_3): 14.12 (q); 22.60 (q); 22.73 (t); 23.04 (q); 23.54 (t); 32.84 (t); 38.80 (t); 42.69 (t); 81.18 (q); 127.19 (d); 127.49 (d); 127.79 (d); 142.17 (s). IR (KBr, cm^{-1}): 3456 (br,s); 3029 (m); 2933 (vs); 2871 (vs); 1465 (s); 1452 (s); 1384 (s); 1345 (s); 1026 (s); 1006 (s); 739 (s); 702 (s). Exact mass for $\text{C}_{15}\text{H}_{24}\text{O}$ requires: M, 220.183; found: M^+ , 220.183. **(S)-(-)-8**: $[\alpha]_{578} -30.5$ ($c=0.55$, CHCl_3); **(R)-(+)-8**: $[\alpha]_{578} +30.4$ ($c=0.58$, CHCl_3). HPLC column: chiralcel OD, solvents: n-hexane(97.5%) / 2-propanol(2.5%), flow speed: 1ml/min. HPLC column: chiralcel OD, solvents: n-hexane(95%) / 2-propanol(5%).

General procedure for the nucleophilic addition of lithium mercaptides to (R)-(-)-1

Under a nitrogen atmosphere, an *n*-butyllithium solution in *n*-hexane (10 mmol) and benzyl mercaptan (0.75 ml, 6.4 mmol) or *n*-butyl mercaptan (0.7 ml, 6.5 mmol) were added to BF₃·OEt₂ (10 mmol) in 16 ml of THF at -78°C. The mixture was stirred for 10 minutes and (R)-(-)-2-phenyl-3,3-dimethyloxetane (R)-(-)-1 (6 mmol) was added immediately. After stirring 30 minutes at -78°C, the reactions were terminated by adding aqueous ammonium chloride and work up was carried out as above. The yields (R)-(-)-9 and (R)-(+)-10 were 75% and 83% respectively.

(1R)-(-)-1-hydroxy-1-phenyl-2,2-dimethyl-4-thiaoctane (R)-(-)-9

¹H-NMR (CDCl₃): 0.91 (s, 3H); 0.93 (t, 3H); 0.99 (s, 3H); 1.44 (m, 2H); 1.59 (m, 2H); 2.55 (m, 4H); 4.66 (s, 1H); 7.32 (m, 5H). ¹³C-NMR (CDCl₃): 13.72 (q); 22.02 (t); 22.34 (q); 23.85 (q); 31.90 (t); 33.96 (t); 39.64 (s); 43.35 (t); 79.59 (d); 127.35 (d); 127.61 (d); 127.70 (d); 141.50 (s). IR (KBr, cm⁻¹): 3448 (br,s); 3029 (w); 2960 (vs); 2929 (s); 2872 (s); 1465 (s); 1452 (s); 1381 (m); 1362 (m); 1040 (s); 1026 (s); 703 (s). Exact mass for C₁₅H₂₄OS requires: M, 252.155; found: M⁺, 252.155; EA, C, 71.38; H, 9.58; S, 12.70; found: C, 71.42; H, 9.60; S, 12.71; [α]₅₇₈ -3.4 (c=0.57, CHCl₃). HPLC column: chiralcel OD, solvents: n-hexane(95%) / 2-propanol(5%).

(1R)-(+)-1-hydroxyl-1,5-diphenyl-2,2-dimethyl-4-thiapentane (R)-(+)-10

¹H-NMR (CDCl₃): 0.91 (s, 3H); 0.99 (s, 3H); 2.22 (s, 1H); 2.45 (d, ²J=12.4Hz, 1H); 2.70 (d, ²J=12.4Hz, 1H); 3.76 (s, 2H); 4.66 (s, 2H); 7.32 (m, 5H). ¹³C-NMR (CDCl₃): 22.44 (q); 23.77 (q); 38.08 (t); 39.64 (s); 42.23 (t); 79.34 (d); 127.00 (d); 127.37 (d); 127.64 (d); 128.49 (d); 128.96 (d); 138.30 (s); 141.50 (s). IR (KBr, cm⁻¹): 3455(br,s); 3062 (s); 3029 (s); 2966 (s); 2928 (s); 2872 (s); 1493 (s); 1452 (s); 1383 (m); 1363 (m); 1269 (m); 1239 (m); 1197 (m); 1041 (s); 1027 (s); 1003 (m); 753 (m); 701 (s); exact mass for C₁₈H₂₂OS requires: M, 286.139; found: M⁺, 286.139; EA, C, 75.48; H, 7.74; S, 11.19; found: C, 75.49; H, 7.74; S, 11.18; [α]₅₇₈ +3.2 (c=0.32, CHCl₃). HPLC column: chiralcel OD, solvents: n-hexane(95%) / 2-propanol(5%).

Acknowledgements

This investigation was supported by DSM Research. We express our appreciation to Dr. L.A. Hulshof of DSM Andeno. We are indebted to Mr. W. Kruizinga, Mr. A. Kiewiet, and Mr. M. Suijkerbuijk for technical assistance.

References

- 1 K. Tani, *Kagaku, Zokan (Kyoto)*, 1986, **109**, 191. Chem. Absts. **107**, 175176.
- 2 E. F. J. de Vries, J. Brussee, C. G. Kruse, A. van der Gen, *Tetrahedron: Asymmetry*, 1994, **5**, 377.
- 3 A. Hirao, H. Mochizuki, S. Nakahama, N. Yamazaki, *J. Org. Chem.*, 1979, **44**(10), 1720.
- 4 A. Alexakis, P. Mangeney, *Tetrahedron: Asymmetry*, 1990, **1**, 477.
- 5 R. Noyori, M. Kitamura, *Angew. Chem. Int. Ed. Engl.*, 1991, **30**, 49.
- 6 S. Jr. Searles, *Heterocyclic Compounds with Three- and Four-Membered Rings*; Weissberger, A., Ed, Interscience, New York, 1964, p983-1068.
- 7 M. Chini, P. Crotti, L. Favero, F. Macchia, *Tetrahedron Letters*, 1994, **35**, 761.
- 8 A. Papini, A. Ricci, M. Taddei, *J. Chem. Soc. Perkin Trans.*, 1984, **1**, 2261.

- 9 M. J. Eis, J. E. Wrobel, B. Ganem, *J. Am. Chem. Soc.* 1984, **106**, 3693.
- 10 R. C. Larock, S. K. Stolz-Dunn, *Synlett*; 1990, 341.
- 11 M. Segi, M. Takebe, S. Masuta, T. Nakajima, S. Suga, *Bull. Chem. Soc. Jpn.* 1982, **55**, 167.
- 12 H. A. Carless, H. S. Trivedi, *J. Chem. Soc. Chem. Comm.*, 1979, 382.
- 13 (a) K. Soai, S. Niwa, T. Yamanoi, H. Hikima, M. Ishizaki, *J. Chem. Soc., Chem. Commun.*, 1986, 1018. (b) M. Segi, M. Takebe, S. Masuda, T. Nakajima, S. Suga, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 167.
- 14 A. Balsamo, G. Ceccarelli, P. Crotti, F. Macchia, *J. Org. Chem.*, 1975, **40**, 473.
- 15 (a) X. Hu, R. M. Kellogg, *Synthesis*, accepted. (b) R. Ebens, *Ph. D. Thesis*, Groningen, 1993.
- 16 (a) A. Balsamo, P. Crotti, M. Ferretti, and F. Macchia, *J. Org. Chem.*, 1975, **40**, 2870. (b) A. Balsamo, C. Battistini, P. Crotti, F. Macchia, *Gazz. Chim. Ital.*, 1978, **108**, 619. (c) P. Crotti, F. Macchia, A. Stoppipni, L. Turbanti, *Gazz. Chim. Ital.*; 1985, **115**, 411.
- 17 S. Searles, C. F. Butler, *J. Am. Chem. Soc.*; 1954, **76**, 56.
- 18 J. A. Faunce, B. A. Grisso, P. Mackenzie, *J. Am. Chem. Soc.*, 1991, **113**, 3418.
- 19 S. Searles, *J. Am. Chem. Soc.*, 1951, **73**, 124.
- 20 G. Buchi, C. G. Inman, E. S. Lipinsky, *J. Am. Chem. Soc.*, 1954, **76**, 4327.
- 21 M. Yamaguchi, Y. Nobayashi, I. Hirao, *Tetrahedron*, 1984, **40**, 4261.
- 22 S. Searles, *J. Am. Chem. Soc.*; 1951, **73**, 4515.
- 23 *Vogel's Textbook of Practical Organic Chemistry*; Fourth edition, Longman, London and New York, 1978, p. 584.

(Received in UK 28 April 1995)